Remarks

I. Rejection of claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, first paragraph.

The Examiner rejected claims 11, 12, 24, 28, 33, 39 and 40 under 35 U.S.C. §112, first paragraph, asserting that the specification, while being enabling for treatment of cancer characterized by p53 loss or deficiency by direct administration Onyx 051 and 053 (comprises a single amino acid substitution in amino acid 240 or 260), does not reasonably provide enablement for any other embodiment. The Examiner asserted that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

A. Applicants Submit the Specification Provides Enablement Commensurate in Scope with the Claimed Subject Matter.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See Ex Parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). A patent may be enabling even though some experimentation is necessary. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988).

In the present application, applicants have clearly enabled one of ordinary skill in the art to make and use the invention commensurate in scope with the claims without undue experimentation. The Examiner's rejection focuses on the assertion that applicants' claims are directed to "any single amino acid mutation in E1B-55K such that binding to p53 is reduced" (Office action, 9 May 2007, page 3). The focus of the Examiner's rejection is further illustrated in the following remarks:

> Hence, applicants have elucidated **the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements**. As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. Hence, the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the El B 55k gene that have lost the ability to

> bind p53 and furthermore be used to treat cancer. (Office action, mailed 9 May 2007, page 5.)

The Examiner has acknowledged that the efficacy of the present invention lies in the treatment of p53(-) tumors and that the efficacy of combined adenoviral/chemotherapy treatment have been specifically observed, for example, as discussed by Kirn, et al. (Office action, mailed 9 May 2007, page 4). Further, the Examiner has acknowledged the efficacy of the methods of the present invention by indicating allowable subject matter.

Kirn, et al., discuss the use of adenovirus mutant *dl*1520 (ONYX-015) in clinical trials for the treatment of a number of cancer types. As discussed by Kirn, et al.:

> *dl*1520 (Onyx-015) was the first adenovirus described to mirror the gene deletion approach pioneered by Martuza with herpesvirus. Bischoff *et al.* (1996) hypothesized that an adenovirus with deletion of a gene encoding a p53-binding protein, E1B-55 kD, would be selective for tumors that already had inhibited or lost p53 function. p53 function is lost in the majority of human cancers through mechanisms including gene mutation, overexpression of p53-binding inhibitors (e.g., mdm2, human papillomavirus E6) and loss of the p53-inhibitory pathway modulated by $p14^{arf}$. (Kirn, et al., page 6653, col. 1.)

In the present application, applicants have isolated and characterized recombinant adenovirus comprising a single amino acid substitution mutation in the E1B-55K gene that reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, wherein the recombinant adenovirus retains late viral function. Applicants were the first to demonstrate that single amino acid mutations were capable of reducing or eliminating E1B-55K protein's ability to bind to the tumor suppressor p53 and that recombinant adenoviruses harboring such single amino acid mutations demonstrated tumor cytotoxicity.

One important advantage of the single amino acid mutations of the present invention resides in the observation that recombinant adenoviruses comprising a single amino acid substitution mutation in the E1B-55K gene resulted in recombinant adenoviruses that had replication capacity in human cancer cells more like wild-type adenovirus versus the attenuated replication capacity of ONYX-015 (see, e.g., specification page 12, lines 10-20). This increased ability to replicate in human cancer cells results in improved tumor cytolytic activity relative to, for example, ONYX-015 (see, e.g., specification, page 23, lines 20-35).

Kirn, et al., provide extensive discussion of the use of adenovirus ONYX-015 alone and in combination with chemotherapy for the treatment of cancer. Kirn, et al., state the following with regard to ONYX-015:

> For the first time since viruses were first conceived as agents to treat cancer over a century ago, we now have definitive data from numerous phase I and phase II clinical trials with a well-characterized and well-quantitated virus. *dl*1520 (Onyx-015, now CI-1042, Pfizer, Inc.) is a novel agent with a novel mechanism of action. This virus was to become the first virus to be used in humans that had been genetically-engineered from replication-selectivity. (Kirn, et al., page 6664, col. 2).

Further, Kirn, et al., discuss the evidence for a potential-synergistic interaction between adenoviral therapy and chemotherapy that has been demonstrated in multiple clinical trials (Kirn, et al., page 6666, col. 1, to 6667, col. 1).

Kirn, et al., conclude:

> Replication-selective oncolytic adenovirus represent a novel cancer treatment platform. Clinical studies have demonstrated the safety and feasibility of the approach, including the delivery of adenovirus to tumors through the bloodstream (Heise *et al.*, 1999b; Reid *et al.*, 1999; Nemunaitis *et al.*, 1999). The inherent ability of replication-competent adenoviruses to sensitize tumor cells to chemotherapy was a novel discovery that has led to chemosensitization strategies. (Kirn, et al., page 6667, col. 2).

In the present application, applicants have consistently compared important phenotypes of ONYX-015 to the replication-selective recombinant adenoviruses of the present invention. Applicants demonstrated that the recombinant adenoviruses of the present invention (i) showed substantially reduced binding of p53 (as does ONYX-015; see specification, Example 2, pages 19-22), (ii) showed protein synthesis profiles more similar to wild-type than to ONYX-015 which is an advantage because generally higher levels of adenoviral replication correspond to increased cytotoxicity in target cells (see, specification, Example 3, pages 22-23), and, consistent with the previous observation, (iii) tumor cell specific cytolytic activity of the recombinant viruses of the present invention was higher than ONYX-015 (see, specification, Example 4, page 23). Thus, it is clear from the data presented by applicants that the recombinant viruses of the present invention provide at least

similar if not superior anti-cancer properties relative to ONYX-015, which has been demonstrated in clinical trials to be useful for the treatment of cancers.

Further, the present specification discusses the combination of the claimed recombinant adenoviruses with chemotherapy (see, e.g., specification, pages 16-17).

Accordingly, as the Examiner has acknowledge AND THE APPLICANTS HAVE CLAIMED, efficacy of the present invention lies in the treatment of p53(-) tumors and, in the claimed embodiments, in combined adenoviral/chemotherapy treatment.

The specification contains extensive teachings regarding making of the recombinant adenoviruses used in the methods of the present invention. Adenovirus E1B-55K protein sequences and nucleic acid coding sequences are well known in the art (see, e.g., specification, pages 1-3; page 6, lines 7-10; page 9, lines 24-32; page 10, line 31 to page 11, line 19; page 12, lines 7-9; Example 1, pages 17-19). Specifically, the region of the E1B-55K protein that mediates its interaction with the p53 protein has been mapped (see, e.g., specification, page 10, lines 31-34). Methods of constructing adenoviral mutants are known in the art (see, e.g., specification, page 11, lines 15-28; page 12, lines 3-9) and specific methods to generate 26 mutants in the E1B-55K protein coding sequence are set forth in Example 1 (see, e.g., specification, pages 17-19). Guidance concerning substitution of amino acids suitable for generating mutant polypeptides is discussed in the specification (see, e.g., specification, page 12, line 21, to page 13, line 23). Tumor cell lines used to conduct screening of recombinant adenovirus are readily available (see, e.g., specification page 11, line 29, to page 12, line 2).

A patent need not teach, and preferably omits, what is well known in the art. *See Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.,* 730 F.2d 1452, 1453, 221 USPQ 481, 489 (Fed. Cir. 1984). *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d at 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

In addition, applicants have provided a disclosure that explicitly describes the methodology for the creation of the recombinant adenovirus of the present invention as well as methods of identifying recombinant adenoviruses having the desired characteristics for use in the practice of the methods of the present invention. Example 1 (see, specification, pages 17-19) describes construction of twenty-five single amino acid substitution E1B-55K mutant

adenoviruses and one mutant having two amino acid substitutions. Each recombinant adenoviruses were generated using a forward primer and a reverse primer. Final products were transformed into XL-1 cells and confirmed by DNA sequencing. Recombinant viruses were constructed by co-transfecting pJM17 with plasmids containing the mutations into 293 cells and were plaque purified to rule out wild-type contamination. Mutations were confirmed by PCR followed by sequencing of the E1B-55K region.

Example 2 (see, specification, pages 19-22) describes evaluation of binding of the isolated E1B-55K mutants with p53. The twenty six mutant adenoviruses produced as described in Example 1 were initially screened to determine their effect on the steady-state levels of p53 in A549 cells. These data suggested that two of the adenoviral E1B-55K mutants, R240A and H260A fail to bind p53. This was confirmed by directly examining the ability of the E1B-55K mutants R240A and H260A to interact with p53 by immunoprecipitation experiments using S^{35}-labeled cell extracts from infected A549 cells.

Example 3 (see, specification, pages 22-23) describes the effects of the E1B-55K mutations on the ability of the recombinant adenoviruses to replicate in target cells. The ability to replicate in target tumor cells generally improves the cytotoxicity of the recombinant adenovirus. At 39°C., all of the viruses replicated to similar extent. The yield of *dl*309 was approximately 4-fold higher than that of ONYX-015, and the yields of ONYX-051 (mutant R240A) and ONYX-053 (H260A) fell in between. At 32°C., however, the ONYX-015 yield was reduced nearly 35-fold compared to that of *dl*309, which is consistent with the previous reports. Replication of ONYX-051 was essentially identical to that of *dl*309, while replication of ONYX-053 was slightly reduced (4-fold). Thus ONYX-051 (mutant R240A) and ONYX-053 (H260A) have an improved ability to replicate in target cells relative to ONYX-015. Further, the protein synthesis profile in cells infected with ONYX-051 (mutant R240A) and ONYX-053 (H260A) was similar to that in cells infected with wild-type viruses *dl*309 and WtD. This observation suggests that ONYX-051 (mutant R240A) and ONYX-053 (H260A) are capable of modulating mRNA trafficking in favor of late viral mRNA nuclear export.

Example 4 describes the cytotoxic activity of recombinant adenoviral E1B-55K mutants. Among the recombinant adenoviruses described in the application, most, including

ONYX-051, were comparable to *dl*309 in their ability to infect and kill tumor cells. In the case of ONYX-053, its tumor cytolytic activity was 35- to 100-fold lower than that of *dl*309, but more active than ONYX-015 by a factor of 4- to 5-fold.

Accordingly, two recombinant adenoviruses were identified out of twenty-six recombinant adenoviruses, using the methods described in the present application, that met the criteria for use in a method of treating cancer as outlined above and discussed relative to the Kirn, et al., reference.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation *See Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). The law does not require the impossible. Hence, it does not require that an applicant describe in his specification every **conceivable** and possible future embodiment of his invention. *See SRI International v. Matsushita Elec. Corp. of America*, 775 F.2d 1107, 1121, 227 USPQ 577 (Fed. Cir. 1985), emphasis in original. Further, the enablement requirement may be satisfied even though some experimentation is required. *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

Accordingly, the specification describes in detail how to make recombinant adenoviruses comprising a single amino acid substitution mutation in the E1B-55K gene, how to determine that the mutation reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, and how to determine the recombinant adenoviruses that retain late viral function. Further, two recombinant adenoviruses were identified out of twenty-six recombinant adenoviruses that met the criteria for use in a method of treating cancer as outlined above and discussed relative to the use of adenovirus ONYX-015 in the Kirn, et al., reference.

Applicants have taught one reasonably skilled in the art to make and use the invention from the disclosures in the application coupled, if necessary, with information known in the art without undue experimentation. Applicants described two specific embodiments of the recombinant adenoviruses of the present invention. It is it not required that applicants describe in the specification every **conceivable** and possible future embodiment of the invention.

Finally, applicants respectfully point out that application USSN 09/918,696, now U.S. Patent No. 6,635,244, is the parent application to the present application, was examined by the same Examiner, and comprises the following granted claims:

> 1. A recombinant adenovirus comprising a mutation in the E1B-55K gene, said gene encoding a mutated E1B-55K protein comprising a single amino acid mutation, said single amino acid mutation reducing the ability of said E1B-55K mutated protein to bind to the tumor suppressor p53 when compared to the wild-type E1B-55K protein and said adenovirus has the further property of retaining late viral function.
>
> 2. A recombinant adenovirus as described in claim 1, wherein said adenovirus is selected from the group consisting of Onyx 051 and Onyx 053.
>
> 3. A recombinant adenovirus as described in claim 2 wherein said adenovirus is Onyx 051.
>
> 4. A recombinant adenovirus as described in claim 2 wherein said adenovirus is Onyx 053.
>
> 5. A recombinant adenovirus as described in claim 1, wherein said adenovirus has a mutation in amino acid 240 or 260.
>
> 6. A recombinant adenovirus as described in claim 1, wherein the replication of said adenovirus is cold insensitive.

As the parent application is now an issued U.S. Patent, the presumption of validity under 35 U.S.C. §282 carries with it the presumption that the Examiner did the Examiner's duty and knew what claims the Examiner was allowing. The recombinant adenovirus in the independent claims of the present application mirror the claim limitations in the independent claims of the granted patent of the parent application. Accordingly, applicants submit that it is completely inappropriate for the Examiner to be questioning the scope of the presently claimed invention based on a question of whether or not one of ordinary skill in the art is capable of "identifying adenovirus with single amino acid mutations in the El B 55k gene that have lost the ability to bind p53" (Office action, mailed 9 May 2007, page 5).

Typically an Examiner will argue that the patentability of each application is determined on its own merits. In the present application, applicants request a substantial response rather than such a *pro forma* response because (i) the patent in question is the parent

application to the present application, (ii) the Examiner for both applications is the same, and (iii) the claim limitations regarding the recombinant adenovirus in the independent claims of the present application mirror the claim limitations in the independent claims of the granted patent of the parent application.

In view of the above arguments, applicants submits that the claims are enabled for the entire scope of the claimed invention. Applicants respectfully request withdrawal of that the rejection of the claims under 35 U.S.C 112, first paragraph.

B. The Examiner Has Failed to Establish a Prima Facie Case of Lack of Enablement Commensurate in Scope with the Claimed Subject Matter.

To support the rejection of the claims for lack of enablement commensurate in scope with the claimed subject matter, the Examiner stated the following:

> The instant invention is unpredictable for treatment of cancer in humans **given the broad recitation of a genus of adenovirus for delivery to p53 lacking neoplastic cells wherein the adenovirus have reduced binding to p53**. The instant invention is based upon the premise that targeted mutations within EIB 55K result in a virus that is replicative in tumor cells lack p53 while normal cells do not. As well the specification teaches that this premise is distinctly connected to the replicative condition of the rAd. However, by recitation that the rAd comprises a single amino acid mutation in EIB 55K, the adenovirus to be used in the treatment encompasses a broad and diverse genus of adenoviruses that need only be linked by a mutation in E1B 55K. Rather the nature of the adenoviruses for treatment of cancer according to the instant invention must be replicative. To this end, applicants generated 26 mutants but only two of these mutants are capable of reduced binding to p53. These mutants (Onyx 051 and 053) comprise a single mutation in amino acid 240 and 260.
>
> **Hence, applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26 produced have the recited functional requirements.** As well, applicants have not provided the structural requirements of the single amino acid mutants such that one of skill in the art would be able to identify those mutants that have lost the ability to bind efficiently to p53. Hence, **the unpredictability of using the claimed invention in gene therapy is accentuated due to the broad and unpredictable nature of the identifying adenovirus with single amino acid mutations in the El B 55k gene that have lost the ability to bind p53 and furthermore be used to treat cancer.** (Emphasis added; Office action, mailed 9 May 2007, page 5.)

Whenever the PTO makes a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicants' claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *See In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Examiner has presented no evidence to support the Examiner's questioning of the objective enablement of the claims by the specification. The discussion presented by the Examiner amounts only to conclusions not supported by any evidence or reasoning supported by the current literature.

On the contrary, applicants provided extensive teachings relating to the generation and identification of recombinant adenovirus comprising a single amino acid substitution mutation in the E1B-55K gene that reduces the ability of the mutated E1B-55K protein to bind to the tumor suppressor p53, wherein the recombinant adenovirus retains late viral function. These teachings were discussed in detail herein above. Further, the teachings of the present specification regarding the properties of the claimed recombinant adenoviruses (for example, reduced binding to p53, retention of late viral function and replication in target cells, and tumor cell cytotoxicity) completely support the method claims of the present invention. As discussed above, the reference of Kirn, et al., also supports use of the recombinant adenovirus of the present invention in methods of cancer treatment, which comprise administering the recombinant adenovirus and administering chemotherapy, as compared with a clinical trials of treatments employing ONYX-015.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation *See Ex parte Forman*, 230 USPQ 546 (P.T.O. Bd. Pat. App. & Int., 1986). Further, the enablement requirement may be satisfied even though some experimentation is required. *See Hybritech Inc. v. Monoclonal Antibodies*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

The Examiner states that "applicants have elucidated the unpredictability of any single amino acid to produce the required functional requirements as only two mutants of 26

produced have the recited functional requirements" (Office action, mailed 9 May 2007, page 5). Once again, this statement is merely a conclusion without any evidence to support it. The Examiner has NOT provided any evidence that teaches that finding 2/26 mutants (or 7.7% of recombinant viruses screened) with the desired characteristics constitutes undue experimentation.

When confronted with a similar pattern of facts in the field of recombinant, molecular biology the Board of Patent Appeals and Interferences (B.P.A.I.) found that the Examiner had not established a reasonable basis for questioning the sufficiency of the supporting disclosure when taken in combination with the relevant state of the art as it related to the claimed invention. In *Ex parte Chen*, 61 USPQ2d 1025 (B.P.A.I. Aug. 22, 2001) (unpublished) the invention as claimed was to a transgenic carp containing an exogenous gene encoding a growth hormone (the rtGH gene) that was operably linked to a promoter. This exogenous rtGH gene was introduced into the carp at an embryonic stage.

Certain claims were rejected by the Examiner who asserted the specification did not disclose a process that was repeatable as to the levels of expression to obtain carp or other fish that expressed the same transgene product, wherein the level of expression was shown to directly affect phenotypic characteristics of the fish. In support of the rejection, the Examiner cited a prior art reference as evidence of a level of unpredictability in this art. The reference taught that there are three steps or factors that must be shown to exist in a true transgenic animal: (1) integration into the host chromosome, (2) expression, and (3) germ-line transmission of foreign genes.

The applicant (Chen) did not dispute the three factor test presented by the Examiner but argued that the specification would meet this test and permit a person skilled in this art to make and use the claimed invention by following the detailed procedures disclosed in applicant's specification. *See Ex parte Chen*, 61 USPQ2d 1025, 1028 (B.P.A.I. Aug. 22, 2001) (unpublished).

Regarding the overall inquiry concerning enablement the B.P.A.I. stated the following:

> We are mindful that the Patent and Trademark Office (PTO) bears the initial burden of providing reasons for doubting the objective truth of the statements made by appellants as to the scope of enablement. Only when the

> PTO meets this burden, does the burden shift to appellants to provide suitable evidence indicating that the specification is enabling in a manner commensurate in scope with the protection sought by the claims. *See Ex parte Chen*, 61 USPQ2d 1025, 1027 (B.P.A.I. Aug. 22, 2001) (unpublished).

The B.P.A.I. reversed the rejections asserted by the Examiner and held:

> In responding to [Chen's] arguments, the examiner urges that the level of experimentation is undue and points to the success rate 1% or 20 out of 1746 attempts for the integration of the gene into the embryos described in the specification. However, **the examiner offers no evidence which would reasonably support a conclusion that one skilled in this art would regard this rate of success for the integration of the rtGH gene as evidencing undue experimentation.** We remind the examiner that some experimentation may be required as long as it is not undue .... [Chen's] **disclosure explicitly describes the methodology** to be used to arrive at the claimed transgenic carp. **As the record now stands, the numbers emphasized by the examiner would reasonably appear to reflect the need for a repetitive procedure, rather than undue experimentation by those wishing to practice the invention**. (Emphasis added, *See Ex parte Chen*, 61 USPQ2d 1025, 1028 (B.P.A.I. Aug. 22, 2001) (unpublished).)

The B.P.A.I. found that the Examiner had not established a reasonable basis for questioning the sufficiency of the supporting disclosure when taken in combination with the relevant state of the art as it related to the claimed invention. The B.P.A.I. reversed the scope rejection under 35 U.S.C. §112, first paragraph.

In the present case, as in *Ex parte Chen*, the Examiner has offered no evidence that would reasonably support the conclusion that one skilled in the art would regard the success rate of 2/26 (~7.7%) of obtaining recombinant adenovirus, having the desired characteristics for use in the practice of the methods of present invention, as evidence of undue experimentation. Particularly in view of the fact that applicants have provided a disclosure that explicitly describes the methodology to be used to arrive at the claimed recombinant adenovirus having the desired characteristics for use in the practice of the methods of present invention. The numbers emphasized by the Examiner appear to do no more than reflect that the specification provides a repeatable procedure, rather than undue experimentation, for use by those having ordinary skill in the art to practice the present invention.

Accordingly, in view of the above arguments, applicants submit that the Examiner

has failed to establish a prima facie case for lack of enablement of the present invention due to undue experimentation.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters that the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact Gregory Giotta at (510) 597-6502 or Gary R. Fabian at (650) 780-9030.

Respectfully submitted,

Date: 9 Oct 2007 By: Gary R Fabian

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